AHA Scientific Statement: Summary of the Scientific Conference on Dietary Fatty Acids and Cardiovascular Health[1]

Conference Summary From the Nutrition Committee of the American Heart Association

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KEY WORDS: • *AHA Scientific Statement* • *diet* • *fatty acids* • *risk factors* • *cardiovascular diseases*

The objective of this Executive Summary is to provide a synopsis of the research findings presented at the American Heart Association conference "Dietary Fatty Acids and Cardiovascular Health—Dietary Recommendations for Fatty Acids: Is There Ample Evidence?" held on June 5–6, 2000, in Reston, Va. The conference was held to summarize the current understanding of the effects of fatty acids on risk of cardiovascular disease (CVD) and cancer, as well as to identify gaps in our knowledge base that need to be addressed. There is great interest in learning more about the biological effects of the individual fatty acids, their role in chronic disease risk, and their underlying mechanisms of action. As research advances are made, there is always the need to question how new findings may be translated into practice. There is a long history of research providing the basis for the modification of existing dietary guidelines. Research findings have been used to verify intake criteria and are considered along with practical issues of implementation to establish new guidelines. A substantive body of consistent evidence sufficient to defend a dietary recommendation or a change in existing dietary guidance is essential. The conference highlighted the progress that has been made in understanding the biological effects of fatty acids and also addressed the need to learn more about how different fatty acids affect the risk of chronic disease, within the context of refining dietary guidance to further enhance health.

EPIDEMIOLOGICAL, CLINICAL TRIAL, AND NONHUMAN PRIMATE EVIDENCE FOR THE RELATIONSHIP BETWEEN TYPE OF FAT AND CORONARY DISEASE

As study designs have become increasingly rigorous, a number of megatrends have emerged from the data (1,2). There is increased emphasis on identifying the type of fat that best correlates with disease end points. The classic studies of Keys et al (3) and Hegsted et al (4) have shown that saturated fatty acids (ie, those with a carbon chain length of C12:0 to C16:0) raise total and low-density lipoprotein (LDL) cholesterol levels, whereas C18:0 and monounsaturated fat (*cis* C18:1) are neutral when substituted for carbohydrate, and n-6 polyunsaturated fatty acids (PUFAs) lower cholesterol (3,4). More recent studies have shown that long-chain n-3 fatty acids are

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hypotriglyceridemic and *trans* fatty acids are hypercholesterolemic. Epidemiological studies have shown that saturated fat intake is associated with increased risk of coronary heart disease; the greatest risk reduction is associated with PUFA intake, and a lesser extent of risk reduction is associated with monounsaturated fat. Both n-6 (linoleic acid) and n-3 (α-linolenic acid) PUFAs are protective. *Trans* fatty acids are strong predictors of increased coronary risk compared with saturated fat or carbohydrates (1).

The paradigm that dietary fats act exclusively via effects on serum lipids and lipoproteins has been challenged (5–8). The Lyon Diet Heart Study (5) and the Indian Heart Study (6) have both shown in clinical trials that diet can prevent fatal and nonfatal cardiovascular events in individuals with CVD. In both trials, saturated fats were replaced with monounsaturated fats and α-linolenic acid, an n-3 PUFA that is present in canola (rapeseed) oil. Vegetables and fruits were increased in the diets in these studies as well. In addition, fish and fish oil have been shown to reduce all-cause mortality (7,8) and cardiovascular death (8) in patients who had myocardial infarction.

Studies have been conducted in primates to examine the effects of dietary fatty acids on atherosclerosis (9,10). Diets with saturated, monounsaturated, and polyunsaturated (including both n-3 and n-6) fatty acids have been evaluated. Coronary artery atherosclerosis (as measured by intimal area) was less in the polyunsaturated fat than in the saturated fat and monounsaturated fat groups. Monkeys fed monounsaturated fat developed equivalent amounts of coronary artery atherosclerosis as those fed saturated fat (9). LDL cholesterol was similar in monkeys fed polyunsaturated and monounsaturated fat and lower than in animals fed saturated fat. However, there was an enrichment of cholesteryl oleate in plasma cholesteryl esters of the monkeys fed the diet high in monounsaturated fatty acids, which correlated with coronary artery cholesteryl ester concentration, a measure of coronary artery atherosclerosis (10). Activation of ACAT2 (the enzyme responsible for cholesterol oleate formation and secretion by the liver) may explain how dietary monosaturated fat promotes atherosclerosis out of proportion to its effects on plasma LDL cholesterol levels. Both n-6 PUFAs (primarily linoleic acid) and n-3 PUFAs (principally eicosapentaenoic acid and docosahexaenoic acid) have been shown to confer protection. That a diet rich in monounsaturated fat resulted in more atherosclerosis than a diet rich in polyunsaturated fat even though plasma LDL and high-density lipoprotein (HDL) cholesterol levels were comparable also suggests that nonlipid risk factors may play a role in atherogenesis. Thus, additional studies with cardiovascular end points that go beyond the measurement of surrogate markers of CVD risk (ie, plasma lipids and lipoproteins) are needed to evaluate the effects of fatty acids in humans. In this regard, there is evidence in human subjects that a single high-fat meal (high in monounsaturated fat or saturated fat) adversely affects endothelial function, (11) which is thought by some to be an early event in the atherogenic process.

EPIDEMIOLOGICAL AND CLINICAL TRIAL EVIDENCE FOR A RELATIONSHIP BETWEEN TYPE OF FAT AND CANCER RISK

There are no good biomarkers for studying the link between cancer risk and fatty acids in the diet (12). Epidemiological studies relating dietary fats to cancer risk have generally shown weak and inconsistent patterns of associations. Breast cancer risk has been shown to be unrelated to fat content of the diet across a wide range of intake. There is limited evidence that monounsaturated fats might be associated with reduced risk and that *trans* fats might be associated with increased risk of breast cancer, but those findings are weak and should be regarded as preliminary. Prostate cancer has been associated with higher dietary saturated fat, an association that may be due to an effect of saturated fat on circulating testosterone levels. Colorectal cancer risk is increased with higher-fat diets, but this association may be due more to a direct effect of red meats or carcinogens formed with high-temperature cooking of meats than to fat per se. There is limited information from randomized, controlled trials of cancer end points. The Polyp Prevention Trial (13) showed that reducing the levels of fat in the diet from 36% to 24% did not reduce the rate of new adenoma formation over a 3-year period. However, because the low-fat group did not show a decrease in plasma cholesterol and HDL cholesterol, established markers of reduced total fat intake, the lack of an effect on polyp formation may have been due to a lack of adherence to the low-fat diet. Additional long-term studies of fatty acids and cancer are needed.

EFFECTS OF FATTY ACIDS ON INSULIN SECRETION AND ACTION

The insulinotropic effect of individual fatty acids increases and decreases dramatically with chain length and degree of unsaturation, respectively (14). According to studies designed to examine the influence of individual fatty acids on insulin secretion in the perfused rat pancreas, insulin release was as follows: octanoate (C8:0), 3.4-fold increase; linoleate (C18:2 *cis*/*cis*), 5.3-fold increase; oleate (C18:1 *cis*), 9.4-fold increase; palmitate (C16:0), 16.2-fold increase; and stearate (C18:0), 21.0-fold increase (14). Insulin release was increased 3.1-fold by palmitoleate (C16:1 *cis*). Only a modest effect on insulin release was observed with a *cis* $\rightarrow$ *trans* switch of the double bond in the C16:1 and C18:1 fatty acids. Thus, there is remarkable diversity in how individual fatty acids affect insulin secretion. Consequently, these in vitro studies suggest that the type and amount of circulating fatty acids may determine the insulin secretory response. Importantly, saturated fat raises insulin resistance. Unpublished data from a multicenter study in Europe showed that individuals were more insulin sensitive when consuming a diet high in monounsaturated fatty acids than when consuming an equivalent diet high in saturated fat.

Increased intake of dietary fat reduces insulin action in experimental animals, and this insulin resistance is associated with the accumulation of triglyceride in muscle and liver. In animal models, high-fat diets composed of fish oil or safflower oil have markedly different effects on insulin action, and these differences may depend on the ability of fatty acids in fish oil to upregulate lipid oxidation in the liver. Mechanisms may involve increased translocation and activation of specific protein kinase C isozymes (PKC-ϵ and PKC-θ) that phosphorylate and reduce the activity of insulin signaling intermediates (15,16). In C2C12 cells (a murine muscle cell line), oleate and palmitate have different effects on insulin-stimulated glucose conversion to glycogen and different effects on key components of the insulin signaling pathways (17). On the other hand, in humans, varying the total fat content of the diet does not affect insulin-mediated glucose disposal (18). However, it is becoming increasingly evident that specific fatty acids or their derivatives may have roles other than as energy substrates involving regulation of enzyme activity and gene expression in insulin-responsive tissues. More in vivo studies in humans are needed.

EFFECTS OF FATTY ACIDS ON HEMOSTATIC FACTORS AND PLATELET FUNCTION

Thrombosis is an important aspect of CVD. The coagulation system, which includes platelets and coagulation proteins, plays a role in the evolution of atheroma and in the events that follow rupture of a plaque that leads to thrombosis and symptomatic disease. As the importance of hemostatic factors has become clear, the question of whether diet may influence them has been one focus of research.

Several hemostatic factors are influenced by dietary components (19,20). For example, when a high-fat diet is replaced by a lower-fat, higher-fiber diet, the activity of factor VII decreases and the capacity of the endogenous fibrinolytic system increases. Studies of the relationship of dietary fatty acids and hemostatic factors generally show that hemostatic proteins are not affected by changes in the type of dietary fat, such as saturated, monounsaturated, *trans*, or n-6 polyunsaturated fats.

Platelets play several roles in atherosclerosis, including exacerbating the atherosclerotic process, adhering to ruptured or eroded lesions, and participating in the formation of an occlusive thrombus. Lipids are an important constituent of the platelet membrane. Lipids are also important in the intracellular signaling of platelets. Many studies have explored the relationship of dietary fatty acids and platelet function. The majority of studies have been performed in small numbers of human subjects and in animal models. However, interpretation of results is difficult because different methods have been used to estimate platelet function, there has been inconsistency in assessment of platelet lipid composition, and there have been questions regarding the relationship of in vitro assays to in vivo activity. The composition and duration of the dietary manipulations have been inconsistent across studies. There are few population-based epidemiological data because of difficulty in assessing platelet function and diet composition in these studies.

In general, the composition of the platelet membrane appears to reflect the fatty acid composition of the diet. Diets rich in n-3 fatty acids appear to cause platelets to aggregate less at a fixed dose of agonist or to require more agonist to aggregate. There are some data to support a deleterious effect of dietary stearic acid on platelet aggregation. It appears that within the context of the usual diet, there may be some effects of dietary fatty acids on both the coagulation proteins and the platelet membrane. However, these effects are minor, and the clinical meaning of such effects is unclear.

EFFECTS OF FATTY ACIDS ON BLOOD PRESSURE

Evidence from laboratory investigations, observational studies, and clinical trials indicates that supplementation of a diet with high doses of n-3 PUFAs (commonly found in fish oil) can reduce blood pressure (21,22). However, large quantities (eg, 3 g per day) are needed to see a minimal effect in nonhypertensive individuals and only very modest effects in hypertensive individuals. The most effective n-3 PUFA is docosahexaenoic acid rather than eicosapentaenoic acid. Given the quantities needed to achieve the desired effect, this is not a practical treatment for lowering blood pressure. Short-term changes in consumption of saturated fat or n-6 PUFAs appear to have little effect on blood pressure, although there is some suggestion that a diet rich in monounsaturated fatty acids can lower blood pressure. Regular fish consumption may also reduce blood pressure; in addition, the effect of fish oil consumption with weight loss is additive in reducing blood pressure.

FATTY ACIDS AND ENDOTHELIAL ACTIVATION

In vitro studies have been conducted to assess the effects of long-chain fatty acids on leukocytic-endothelial interactions that play a role in atherogenesis and inflammation (23). These interactions are mediated importantly by factors that regulate expression of leukocyte adhesion molecules. There is recent evidence that the n-3 fatty acid docosahexaenoic acid reduces endothelial expression of vascular cell adhesion molecule-1 (VCAM-1), E-selectin, intercellular adhesion molecule-1 (ICAM-1), interleukin 6 (IL-6), and IL-8 in response to exposure to IL-1, IL-4, tumor necrosis factor, or bacterial endotoxin (23). In contrast, saturated fatty acids had no inhibitory effects. In addition, there was a progressive increase in inhibitory activity with fatty acids of the same chain length but increasing in degree of unsaturation. Thus, n-3 fatty acids seem to have the greatest inhibitory effect, with n-6 fatty acids being intermediate, followed by monounsaturated fatty acids. The emerging evidence suggests that with increasing fatty acid unsaturation, there is an accompanying increase in inhibition of endothelial activation.

DIETARY FAT INTAKE

The US Department of Agriculture has been monitoring consumption patterns in the United States for over 50 years using representative samples of the population (24). Consumption trends over the past 30 years have shown a general downward trend in energy consumption from 1965 to 1995. This downward trend in energy intake has been paralleled by a decrease in the percent of energy provided by total fat and saturated fat in the diet. When the period 1989 to 1991 is compared with 1994 to 1996, the data show a slight upward trend in energy consumption for certain age/gender groups; it is unclear how much of this is a result of a more accurate measurement as opposed to a true increase in kilocalorie intake. Some differences across racial/ethnic and socioeconomic groups were noted: blacks had a slightly higher intake of total fat and saturated fat intake, and there was a modest decrease in fat and saturated fat intake with increasing income.

Because of challenges associated with collecting accurate food consumption data, there is a pressing need to identify reliable markers of fat and fatty acid intake. Evidence indicates that adipose tissue fatty acid composition is a suitable biomarker for habitual type of dietary fat intake (25,26).

MODIFICATION OF OILS FOR IMPROVED HEALTH BENEFITS

The production of genetically modified oilseed crops to provide vegetable oils with modified lipids provides a convenient mechanism to deliver healthier products to consumers without requiring them to make significant dietary changes (27). Examples of such modified oils include low-saturated fat and zero-saturated fat soybean and canola oils, canola oil that contains medium-chain fatty acids, high-stearate canola oil (for *trans* fatty acid–free products), high oleic acid soybean oil, and canola oil containing the long-chain PUFAs, γ-linolenic (18:3 n-6) and stearidonic acids (18:4 n-3). Long-chain n-3 fatty acids in the form of stearidonic acids, the 18:4 n-3 precursor to eicosapentaenoic acid and docosahexaenoic acid,

could provide a more effective n-3 fatty acid than α-linolenic acid. In addition, vegetable oil–derived stearidonic acids could be used as an alternative to fish oil to provide long-chain n-3 fatty acids with enhanced stability and taste that can be incorporated into a wide variety of foods.

DIETARY FAT RECOMMENDATIONS: WHERE WE ARE AND WHERE WE COULD GO

Current dietary guidance in general recommends a diet that contains ≤30% of energy as fat, ≤10% of energy as saturated fatty acids, up to 10% of energy as PUFAs, and <300 mg of cholesterol per day (28-30). These recommendations are coupled with guidance on physical activity and weight maintenance and are distinct from those for individuals with specific metabolic profiles that might necessitate more restrictive or targeted regimens. In the current revisions of the recommendations, increased recognition is placed on the diet as a whole and away from segmented guidance on individual dietary components. In effect, this shifts the emphasis from the question of what not to consume to what to consume. A more comprehensive approach to dietary guidance will likely reduce the risk of overemphasis on one component of the guidelines over another, allow for a stronger message regarding other aspects of lifestyle (eg, body weight maintenance and regular exercise), and support the necessity of the dietary guidelines/lifestyle approach to disease risk reduction as a lifelong endeavor.

CONCLUSION

Individual fatty acids have remarkably diverse effects on risk factors for CVD. With respect to effects on lipids and lipoproteins, we have a reasonably good understanding of the effects of individual fatty acids. Much remains to be learned about individual fatty acids with regard to other risk factors such as hemostatic factors, platelet function, blood pressure, and endothelial function, as well as the development of atherosclerosis. In general, the unsaturated fatty acids (excluding *trans* fatty acids) favorably affect a number of factors that are cardioprotective. Unsaturated fatty acids lower total and LDL cholesterol levels when substituted for saturated fatty acids (C12:0 to C16:0). Long-chain n-3 fatty acids from fish oil decrease triglyceride levels, favorably affect platelet function, and decrease blood pressure slightly in hypertensive individuals. Oleic acid has been shown to decrease postprandial factor VII activity. Epidemiological studies have shown beneficial effects of unsaturated fatty acids (both polyunsaturated and monounsaturated) compared with saturated fatty acids on incidence of coronary disease. Controlled clinical trials have demonstrated beneficial effects of diets high in n-6 and n-3 fatty acids on coronary heart disease. There is some evidence to suggest potentially adverse effects of unsaturated fatty acids in that monounsaturated fat has atherogenic effects in monkeys that are comparable to those of saturated fat.

Technologies are emerging that will enable the production of designer fats and oils that have a modified fatty acid profile that provides both nutritional and processing benefits. Based on a large body of evidence, it is apparent that the optimal diet for reducing risk of chronic diseases is one in which saturated fatty acids are reduced and *trans* fatty acids from manufactured fats are virtually eliminated. Because of the growing health benefits recognized for unsaturated fatty acids, it is likely that a mixture of these fatty acids in the diet will confer the greatest health benefits within the context of a total fat intake that is considered moderate. Given the limited amount of evidence to date on the effect of individual fatty acids on many of the variables discussed in this meeting summary, it is not possible to incorporate specific advice on all the points raised into population-wide dietary guidelines. As the evidence base strengthens, it will be important to reevaluate the current guidelines on a regular basis and modify them, if necessary, in light of substantive new findings.

APPENDIX

Fatty Acids Conference, June 5 to June 6, 2000, Reston, Virginia: Faculty

Welcome/Opening Remarks, Discussant: Penny Kris-Etherton, PhD, Distinguished Professor of Nutrition, Penn State University, University Park, Pa.

Welcome/Opening Remarks, Discussant, and Conference Discussion (Closing): Robert H. Eckel, MD, University of Colorado, Health Sciences Center, Division of Endocrinology, Denver, Colo.

Overview: Rationale for Dietary Fat Guidelines: Scott M. Grundy, MD, PhD, University of Texas Southwestern Medical Center at Dallas, Dallas, Tex.

Analysis and Interpretation of the Epidemiological and Clinical Trial Scientific Evidence for Fatty Acid Relationships/Effects on Disease End Points: Thomas A. Pearson, MD, PhD, Department Chair, Community and Preventive Medicine, Albert D. Kaiser Professor, University of Rochester, Rochester, NY.

Epidemiological and Clinical Trial Evidence for the Relationship Between Type of Fat and CVD Risk: Frank Sacks, MD, Associate Professor of Nutrition, Harvard School of Public Health, Department of Nutrition, Boston, Mass; Tim Byers, MD, Professor, Department of Preventive Medicine and Biometrics, University of Colorado School of Medicine, Denver, Colo.

Fatty Acids in Atherosclerosis: Lawrence L. Rudel, PhD, Department of Pathology, Wake Forest University School of Medicine, Section of Comparative Medicine, Winston-Salem, NC.

Effects of Fatty Acids on Lipids and Lipoproteins: Margo A. Denke, MD, Associate Professor, University of Texas Southwestern Medical Center at Dallas, Dallas, Tex.

General Discussion and AHA Dietary Guidelines: Ronald M. Krauss, MD, Senior Scientist and Head of the Molecular Medicine Department, University of California at Berkeley, Lawrence Berkeley National Laboratory, Berkeley, Calif.

Insulin Secretion: Daniel T. Stein, MD, Albert Einstein College of Medicine, Bronx, NY.

Insulin Action: Greg Cooney, PhD, Senior Research Fellow, Metabolism and Diabetes Program, Garvan Institute of Medical Research, St. Vincent's Hospital, Sydney, Australia.

Hemostatic Factors: Peter Marckmann, MD, DSc, Associate Professor, Research Department of Human Nutrition, The Royal Veterinary and Agricultural University, Frederiksberg, Denmark.

Platelet Function: Russell P. Tracy, PhD, Professor of Pathology and Biochemistry, Director, Laboratory for Clinical Biochemistry Research, University of Vermont, Colchester, Vt.

Vascular Reactivity: Robert A. Vogel, MD, Herbert Berger Professor of Medicine and Head, Division of Cardiology, Department of Medicine, University of Maryland School of Medicine, Baltimore, Md.

Blood Pressure: Lawrence J. Appel, MD, MPH, The Johns Hopkins University, Baltimore, Md.

Fatty Acids in the Diet and Food Supply: Eileen Kennedy, DSc, United States Department of Agriculture, Office of Research, Education & Economics, Washington, DC.

Biomarkers to Assess Fatty Acid Intake: Hannia Campos,

PhD, Assistant Professor, Harvard School of Public Health, Department of Nutrition, Boston, Mass.

New Technologies to Manipulate Dietary Fatty Acids: Virginia Ursin, PhD, Nutrition Sector, Monsanto Company, Calgene Campus, Davis, Calif.

Technologies to Modify Fatty Acids: Mike Rudrum, PhD, Unilever Research Vlaardingen, Vlaardingen, The Netherlands. *Discussant:* Barbara V. Howard, PhD, President, Medlantic Research Institute, Washington, DC.

Dietary Recommendations for Fatty Acids: Peter L. Zock, PhD, Wageningen Center for Food Sciences, Nutrition and Health Program, Wageningen University, Wageningen, The Netherlands.

Dietary Recommendations for Fatty Acids: Gabriele Riccardi, MD, Institute of Internal Medicine and Metabolic Diseases, Second Medical School, University of Naples, Napoli, Italy.

Recommendations for Dietary Fat: Where We Are and Where We Could Go: Alice H. Lichtenstein, DSc, Professor of Nutrition, HNRC/Tufts University, Boston, Mass.

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